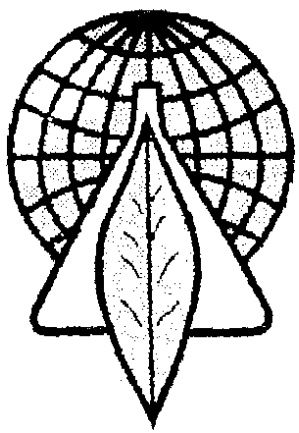
Recent Advances in Tobacco Science

Volume 20

Highlights of Current Research on
Tobacco and Tobacco Chemistry

Proceedings of a Symposium Presented at the 48th Meeting of the
Tobacco Chemists' Research Conference



September 25-28, 1994
Koury Convention Center
Greensboro, North Carolina USA

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NICOTINE UPTAKE AND METABOLISM IN SMOKERS

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ABSTRACT

Accounting for nicotine uptake in smokers has been difficult in the past primarily due to a limited understanding of nicotine metabolism and lack of comprehensive analytical methods. Recent advances in analytical methodology have increased our understanding of nicotine transformations in the body. This presentation reviews work by us and others to determine nicotine disposition and fate in smokers. Nicotine metabolism is now known to involve extensive phase I and phase II reactions and we can account for approximately 90% of nicotine uptake in smokers by summing urinary nicotine and its metabolites. This allows more accurate determination of how much nicotine smokers actually receive when smoking *ad libitum* over a 24 h period. A variety of analytical approaches have been developed to determine nicotine and its metabolites. We demonstrate an application to account for nicotine uptake in smokers of cigarettes with different FTC

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yields. Nicotine uptake was studied in 33 smokers that spanned four FTC "tar" groups: 1 mg "tar" (1MG), ultra-low "tar" (ULT), full-flavor low "tar" (FFLT), and full flavor (FF) cigarette smokers. These categories had mean FTC nicotine yields of 0.14, 0.49, 0.67 and 1.13 mg/cigarette, respectively. Nicotine uptake was determined by monitoring nicotine and its metabolites in 24 h urine samples. The results showed that lower FTC yield cigarettes result in not only less nicotine uptake per 24 h period, but also per cigarette smoked. We conclude from these data that, while FTC yield cannot precisely predict nicotine uptake for an individual smoker, it is useful in predicting and comparing average nicotine uptake by smokers who select cigarettes with a particular FTC yield.

INTRODUCTION

Nicotine uptake and metabolism in humans is a complex process that results in excretion of numerous metabolites [1]. Accounting for total nicotine uptake in smokers has been difficult in the past primarily due to a limited understanding of nicotine disposition and metabolism in humans and lack of comprehensive analytical methods. This presentation reviews work by us and others to determine nicotine uptake and metabolism in smokers.

Several analytical methods have been developed in the pursuit of nicotine metabolites and this review will briefly note some of them. As methods approach total accountability of nicotine absorbed by smokers, an obvious application of these tools is to address the issue of how much nicotine smokers actually absorb from cigarettes. We give an example where four groups of smokers were studied and the results compared with FTC machine-based predictions of nicotine uptake.

Recent Advances in Understanding Nicotine Metabolism.

An extensive review of nicotine metabolism was done in 1991 at an important time in this field [1]. For example, it was only in the late 1980s that *trans*-3'-hydroxycotinine was reported to be a major urinary metabolite in humans [2, 3]. Later still, the existence of significant quantities of conjugated forms of nicotine and its metabolites was discovered [4-9]. These "missing" metabolites naturally limited attempts to account for total nicotine uptake by monitoring urinary excretion of nicotine and its metabolites in smokers. Much progress has been made in the last few years in identifying and quantifying nicotine metabolites. Nicotine metabolism is now known to involve extensive phase I (functionalization changes to the xenobiotic) and phase II (conjugation of the xenobiotic with an endogenous compound) reactions. Recent literature suggests the nicotine metabolic scheme in humans shown in Figure 1 [10-12]. Although not exhaustive in scope, this scheme accounts for all major and several minor nicotine metabolites.

Nicotine metabolism is mediated by different enzymes in the body. Nicotine-N'-oxide is produced exclusively as the

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trans form in humans by a flavin-containing monooxygenase (FMO) [11, 13]. Nicotine-N-glucuronide is formed presumably through the action of UDP-glucuronosyltransferase. Both of these direct products are excreted unchanged and are also formed by human hepatocytes *in vitro* [14]. The most significant metabolic pathway for nicotine is mediated through cytochrome P450 isozymes that produce the nicotine iminium ions shown [15-18] with nicotine-1',5'-iminium ion predominating [11]. Formation of nicotine-1',2'-iminium ion (not shown) has been postulated [19]; however, recent evidence suggests it is not present in smokers' urine [20, 21]. Nicotine-1',5'-iminium ion is converted by aldehyde oxygenase to cotinine [13]. Cotinine is extensively metabolized to its glu-

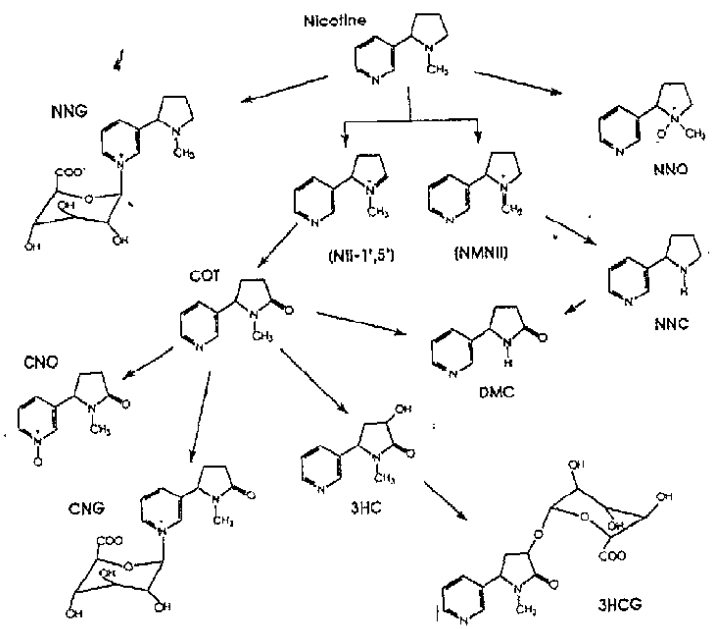

Figure 1. Proposed scheme for nicotine metabolism in humans. NII-1',5' is nicotine-1',5'-iminium ion and NMNII is N-methylene nicotine iminium ion. Other abbreviations are those used in Table I.

TABLE I. Distribution of nicotine and its metabolites in eleven smokers from reference 12. Data are given as percent of total amount detected. Abbreviations refer to those in Figure 1.

Metabolite	% of total excreted
trans-3'-Hydroxycotinine (3HC)	35 ± 8%
Cotinine-N-glucuronide (CNG)	17 ± 7%
Cotinine (COT)	13 ± 4%
Nicotine (unmetabolized)	10 ± 4%
trans-3'-Hydroxycotinine glucuronide (3HCG)	9 ± 4%
Nicotine-N'-oxide (NNO)	7 ± 3%
Cotinine-N-oxide (CNO)	4 ± 2%
Nicotine-N-glucuronide (NNG)	3 ± 2%
Demethylcotinine (DMC)	2 ±<1%

curonide conjugate, to cotinine-N-oxide, and presumably to *trans*-3'-hydroxycotinine, though none of this major urinary metabolite was found in human hepatocytes incubated with nicotine [14]. A minor amount of nicotine is converted to its N-methylene iminium ion to produce nornicotine [22] and possibly norcotinine as shown. The N-glucuronide conjugates of nicotine and cotinine have been determined by direct methods [8, 9, 23]. It has been reported that *trans*-3'-hydroxycotinine is glucuronidated on the hydroxyl oxygen as shown in Figure 1 [24].

The urinary distribution of the major and some minor metabolites is shown in Table I and is based on a study of eleven smokers [12]. *trans*-3'-Hydroxycotinine was the most abundant urinary metabolite followed by cotinine-N-glucuronide and cotinine. Glucuronide conjugates accounted for approximately 30% of all detected metabolites and unmetabolized nicotine found in smokers' urine. Large interindividual variability was observed among smokers in both the total amount of nicotine excreted and the relative abundances of metabolites. This variability makes it difficult to determine total nicotine absorption based on the measurement of a single metabolite. As methods evolved to determine most of the metabolites, assessing total nicotine uptake by monitoring uri-

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nary excretion of nicotine and its metabolites became more feasible.

Analytical Methods for Determining Nicotine and its Metabolites.

Many different methods have been used for determination of nicotine and cotinine in biological fluids but only a few laboratories have reported methods that determine nicotine and its major metabolites (*trans*-3'-hydroxycotinine, cotinine, and their respective glucuronide conjugates) and several minor ones. Gas chromatography (GC) has been reliably used for some time to determine nicotine and cotinine in biological fluids [25-27]; however, some of the nicotine metabolites such as nicotine-N'-oxide and the phase II metabolites are thermally unstable and not suited to direct analysis by GC. Some analytical schemes using GC have been expanded and important metabolites such as nicotine-N'-oxide [28] and *trans*-3'-hydroxycotinine [7] have been added in separate analyses that involve derivatization. An excellent GC method has been developed that accounts for nicotine and its two major urinary metabolites, cotinine and *trans*-3'-hydroxycotinine, in a single chromatographic analysis [29]. This method, in conjunction with hydrolysis to free conjugated compounds, provides a means of accounting for almost all nicotine absorbed by smokers. High performance liquid chromatography (HPLC) has been used to determine nicotine and cotinine in biological samples without derivatization [30-37]. HPLC methods used in conjunction with derivatization with 1,3-diethyl-2-thiobarbituric acid have been used to determine nicotine and up to twelve metabolites in the urine of smokers [38-41]. A powerful method developed in our laboratory combines HPLC with the specificity of thermospray mass spectrometry [42] and has been applied to study nicotine uptake and metabolism in smokers [12]. As in the GC method mentioned above, when used in conjunction with hydrolysis to free conjugated compounds, almost all of the nicotine aborbed by smokers can be determined by this LC/MS method. Specific HPLC methods for the glucuronide conjugates of cotinine and nicotine have been developed in order to confirm their structure and provide

direct methods of analysis [9, 14, 24, 43]. Immunoassay methods, though limited in the number of metabolites they can determine, have proven sensitive to nicotine and its metabolites [44-46]. Cross-reactivity of cotinine antibodies with other nicotine metabolites has been quantified [47, 48]. As research continues in this area, it is possible that antibodies very specific to certain metabolites will be developed.

Determination of Total Nicotine Uptake by Smokers

Determination of total nicotine uptake by smokers is a significant investigative tool and can be used to compare how much nicotine smokers absorb with what would be predicted by machine-based ratings. In the absence of analytical methods, nicotine uptake by cigarette smokers may be thought to be a function of the product yield as determined by the Federal Trade Commission (FTC) machine smoking method. The current FTC method, adopted by the U. S. government in 1967 [49], is based on measurements from a smoking machine following a well-defined regimen of a 35 mL puff of 2 s duration every 60 s [50]. The reference method was established for product comparison although prolonged use of FTC ratings has apparently fostered the belief in some that these data may predict nicotine uptake by individual smokers. Like any standardized machine smoking method, the FTC method suffers from the fact that humans do not necessarily smoke like machines and a prediction of smoke exposure based on the FTC method is only a rough estimate for an individual smoker. Nicotine uptake by smokers is not only influenced by product composition and design, but also by smoker-controlled parameters (puffing patterns, depth of inhalation, number and frequency of cigarettes, etc.) and physiological factors such as pH of mucosal membranes [51, 52]. Subjective factors (such as mood) may also influence smoking behavior so that an individual may smoke each cigarette differently. Given all these considerations, it is unlikely that any machine-based smoking method could accurately predict nicotine uptake for a particular smoker at a particular time for a specific cigarette. In order to put machine-based nicotine uptake predictions in perspective, it would be necessary to measure the actual nicotine uptake by a

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smoker and compare that with predicted machine values.

A method to estimate daily nicotine uptake using metabolic clearance data obtained after intravenous infusion of nicotine and from blood and urinary nicotine concentration data was developed by Benowitz and Jacob [53]. This method was comprehensive in estimating daily nicotine but required subject retention in a clinical ward, a factor that may have influenced the results due to additional stress or other variables related to confinement. Nevertheless, this method has provided useful data in studying nicotine uptake from numbers of cigarettes smoked [54], nicotine pharmacokinetics [55], and nicotine uptake from cigarettes versus the transdermal patch [56]. Similar results have also been obtained using blood cotinine measurements to estimate nicotine uptake [57].

A better approach would determine total nicotine uptake using noninvasive sampling, little or no confinement of the subjects, and little or no variation in normal daily tasks. Smoking is a habit that is part of a daily routine and the less impact a study has on a subject's routine, the more likely it is to reflect normal smoking behavior, and thus, normal nicotine uptake. Pharmacological studies of smoking have demonstrated that nicotine exposure is not intermittent, but rather a 24 h per day exposure due to its accumulation in the body [58]. Active smokers achieve a steady-state level of nicotine in the body that diminishes only during sleep periods. Thus, an ideal method for nicotine uptake would monitor all output of nicotine and its various metabolic forms over a normal 24 h period for a smoker. This point brings us back to urinary excretion of nicotine and its metabolites and advances in analytical methodolgy described above.

A review of quantitative analytical methods shows that very high percentages can be achieved for total nicotine uptake. Kyerematen et al., using radio-labeled nicotine, demonstrated that recovery was greater than 80% in humans by monitoring nine metabolites, two of which had not previously been identified at that time [6]. Benowitz has shown that major phase I metabolites along with unmetabolized nicotine account for approximately 65% of absorbed nicotine in smokers [59]. Curvall et al. demonstrated that a large portion

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of nicotine metabolism is through phase II processes and that the free and conjugated forms of nicotine, cotinine, and 3′-hydroxycotinine, along with the N-oxides of nicotine and cotinine, account for more than 90% of absorbed nicotine [7]. Therefore, methods that determine both phase I and phase II urinary metabolites of nicotine and include minor metabolites such as nicotine-N′-oxide approach total nicotine accountability. Such high recoveries in urine offer the best means for precise quantitation of nicotine uptake in humans [27, 59].

We have incorporated recent understanding of nicotine metabolism into a strategy for determining daily nicotine uptake in smokers. It can be assumed that, on a daily basis, an habitual smoker reaches a steady state of nicotine. Consequently, the amount of nicotine uptake is equal to the amount of nicotine and its metabolites excreted by the smoker. From total nicotine output in 24 h urine samples and the number of cigarettes smoked per day, we can estimate a nicotine uptake value that reflects what the smoker absorbs, on average, from each cigarette. This integrated value naturally accounts for smoking behavior variations during the day. Analysis of 24 h urine specimens to determine daily nicotine uptake by smokers has the advantage of being noninvasive and permits *ad libitum* smoking by subjects with minimal impact on their daily routines.

To better understand the relationship between FTC nicotine yields and actual nicotine uptake in smokers, we applied the above methodology to study nicotine uptake in 33 smokers that spanned four product groups: 1 mg "tar" (1MG), ultra-low "tar" (ULT), full-flavor low "tar" (FFLT), and full flavor (FF) cigarette smokers. These cigarette categories had mean FTC nicotine yields as listed in Table II. The subjects all smoked their usual cigarette brand *ad libitum* and submitted a 24 h urine sample for total nicotine uptake determination during a period for which the number of cigarettes smoked was recorded.

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MATERIALS AND METHODS

Subjects

Thirty-three adult volunteers with an age range of 26 to 50 years participated in this study. Subjects received compensation for their participation. The subjects were all male Caucasians except for two females in the FF group, one Caucasian and one African-American. All subjects were instructed to smoke their usual brand of cigarette (cigarettes were not supplied to the smokers by the experimenters) as much as they desired, record the number of cigarettes smoked, and collect all their urine over a 24 h period. Table II lists the subjects by the type of cigarette they smoked. Each group was studied separately and the FTC nicotine ratings in Table II were taken from the Tobacco Institute Testing Laboratory Report [60]. The 1MG and ULT smokers recorded the number of cigarettes smoked daily over a one week period and submitted three consecutive 24 h urine samples on the final three days of that week. The FFLT and FF smokers recorded the number of cigarettes smoked for one to three days and collected a single 24 h urine sample on the final day.

Apparatus

Each subject was supplied with two polyethylene 3 liter screw-capped specimen bottles (Fisher Scientific, Pittsburgh, PA). The bottles were stored in a portable cooler (Coleman Personal 16, Coleman Co., Inc., Wichita, KA) with a reusable ice substitute (Igloo Corporation, Houston, Texas) to retard bacterial growth. The subjects kept the coolers with them during the 24 h period as they performed their normal routines (work, domestic duties, hobbies, etc.). Total 24 h urine volume was measured immediately after each collection. Samples were frozen at -20° C prior to analysis.

Procedure

Samples for the 1MG, FFLT, and FF smokers were prepared and analyzed according to a modification [12] of a published LC/MS method [42]. The ULT smoker samples were analyzed by a modification [61] of a published GC/MS method [29]

shown to give comparable nicotine uptake data to the LC/MS method. In both methods, nicotine and metabolite concentrations were summed to produce a total nicotine concentration. This value was multiplied by the 24 h urine volume to give the total amount of nicotine uptake for 24 h. The daily nicotine uptake divided by the number of cigarettes smoked gave the nicotine uptake per cigarette.

The data were statistically analyzed by several methods. Paired t-tests were used to compare FTC and measured yields per cigarette for separate groups and all smokers together. The groups were also compared using Duncan's Multiple Range Test. Regression analysis was used to test for the existence of a linear relationship between FTC yield and measured nicotine uptake. The group means were compared with each other to find further significant differences in nicotine uptake that might be expected as a function of FTC yield. Finally, the correlation between nicotine uptake and number of cigarettes was determined. Significance was defined as $P \leq 0.05$.

RESULTS

Group averages for nicotine uptake are presented in Table II with groupings based on FTC yield category. Nicotine uptake is reported on a per cigarette (mg/cig) and daily (mg/24 h) basis. The number of cigarettes and nicotine uptake data

TABLE II. Comparison of FTC nicotine yield with measured nicotine uptake ±SD for four groups of smokers arranged by FTC yield category.

Group	N	cig/24 h	FTC Nicotine Yield		Measured Nicotine Uptake		Ratio of Measured to FTC Yield
			mg/cig	mg/24 h	mg/cig	mg/24 h	
1MG	9	35 ± 16	0.14 ± 0.01	4.8 ± 2.2	0.23 ± 0.11	9.1 ± 7.3	1.64 ± 0.82
ULT	13	37 ± 21	0.49 ± 0.06	16.7 ± 12.5	0.56 ± 0.23	19.2 ± 10.0	1.18 ± 0.53
FFLT	6	37 ± 14	0.67 ± 0.07	24.8 ± 8.3	0.60 ± 0.18	21.8 ± 9.4	0.89 ± 0.28
FF	5	34 ± 15	1.13 ± 0.15	38.1 ± 15.2	1.19 ± 0.43	37.3 ± 14.4	1.04 ± 0.34

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per 24 h were based on a three day average for the 1MG and ULT smokers and on a single day for the FFLT and FF smokers. The FTC nicotine in mg/24 h was calculated from the number of cigarettes smoked multiplied by the FTC nicotine yield in mg/cigarette. These FTC values are compared in Table II with the measured nicotine uptake as mg/24 h and also as mg/cigarette calculated by dividing the measured mg/24 h value by the number of cigarettes smoked. In order to compare actual versus predicted nicotine uptake, the daily amount of nicotine uptake measured and that predicted by FTC yield is expressed as a ratio.

An overview of Table II suggests large variation in smoking behavior as reflected in nicotine uptake and number of cigarettes smoked. There was a broad range of daily nicotine uptake within each group (1-22 mg for 1MG, 4-42 mg for ULT, 13-38 mg for FFLT, and 21-60 mg for FF) with slightly narrower relative ranges when corrected for number of cigarettes smoked (0.06-0.37, 0.16-0.82, 0.37-0.86, and 0.63-1.62 mg/cigarette, respectively). The average number of cigarettes smoked per day was fairly consistent among the groups, ranging from 34 to 37. The average ratios of measured nicotine uptake to FTC nicotine yield as listed in Table II were near unity for FF, FFLT, and ULT smokers, but increased to 1.64 for the 1MG smokers. Although 1MG smokers as a group tended to exceed FTC predictions more than the others, they still received significantly less nicotine on average compared to the other groups on a per cigarette and on a daily basis. Twenty-one of the 33 smokers (64%) in this study absorbed more than the FTC predicted yield of nicotine and 12 (36%) received less.

Measured nicotine uptake in mg/cigarette was compared to the FTC yield using a paired two-tailed t-test and the results are shown in Table III. Mean differences were insignificant for all smokers and the individual groups; however, probability of difference increased as the group FTC yield decreased with 1MG smokers approaching the significance limit of $P = 0.05$. These results show that the FTC nicotine yield was not different from the measured nicotine uptake based on the level of variability and the number of subjects tested.

Nicotine uptake among the four groups was compared on

TABLE III. Probabilities (P) from paired two-tailed t-test used to compare FTC mg/cigarette and measured mg/cigarette. Means are significantly different when $P < 0.05$.

GROUP	N	P
1MG	9	0.065
ULT	13	0.302
FFLT	6	0.654
FF	5	0.809
All	33	0.265

TABLE IV. Results of Duncan's Multiple Range Test for comparing the four different groups in this study. Means with the same letter are not significantly different.

Comparison of mg nicotine/24 h:

Group	N	Mean	Duncan, Grouping
1MG	9	9.1	A
ULT	13	19.2	A B
FFLT	6	21.8	B
FF	5	37.3	C

Comparison of mg nicotine/cig:

Group	N	Mean	Duncan, Grouping
1MG	9	0.23	A
ULT	13	0.56	B
FFLT	6	0.60	B
FF	5	1.19	C

a per cigarette and daily basis using Duncan's Multiple Range Test. The results, summarized in Table IV, showed significant difference between the FF smokers and all other groups with respect to daily and per cigarette nicotine uptake. The ULT and FFLT smokers showed no significant difference from each other in either category which is not surprising since the average FTC yields of these two groups are not very different in this study. Both ULT and FFLT smokers were different from 1MG smokers on a per cigarette basis but only FFLT were different from 1MG in daily nicotine uptake.

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Assessment of linearity between FTC yield and measured nicotine uptake tested for correlation between these variables, I. e., do larger nicotine uptake values result when subjects smoke cigarettes of higher FTC yield? The data are plotted as a function of FTC yield in Figure 2. Figure 2a shows nicotine uptake as mg/24 h for the individual smokers and Figure 2b displays the averages and standard deviations for each product group. Linear regression analysis of the data was performed and the results are listed on each plot. These plots reflect the wide variations of nicotine uptake within each group of smokers. This variability is somewhat diminished when nicotine uptake values are normalized to the number of cigarettes smoked as shown in Figures 2c and 2d. And yet, the group means for nicotine uptake show a significant linear relationship with the FTC nicotine yield ($P < 0.05$) for both nicotine uptake per 24 h and per cigarette. Note that the slopes in these plots are positive, indicating an increasing relationship with FTC yield.

The correlation between measured nicotine uptake and number of cigarettes smoked was determined. These two parameters were highly correlated for 1MG smokers (Pearson $R = 0.94$). These two parameters were less correlated for FFLT smokers ($R = 0.59$), FF smokers ($R = 0.45$), and ULT smokers ($R = 0.38$).

DISCUSSION

The data in this study represent integrated averages of nicotine uptake in smokers over a routine 24 h period. Measuring total nicotine uptake for 24 h, instead of nicotine absorbed from a few cigarettes in a laboratory setting, accounts for a wider range of smoking behavior and achieves a more accurate measure of nicotine absorption by smokers from their self-selected brand of cigarettes during the course of a normal day.

A key assumption in studies such as the one described here is that the method accounts for essentially all nicotine absorption. It is unlikely that 100% is found in each smoker through these metabolites since other minor metabolites of

nicotine are known or postulated in humans [1]. As mentioned previously, it has been estimated that methods such as ours recover more than 90% of the nicotine absorbed [7]. With regard to our data, raising the values by 10% or less would have negligible impact on the relative rankings.

The data clearly show wide variability in nicotine uptake among smokers of the same type of cigarette. Some smokers absorb more, and others less, than the amount of nicotine predicted by the FTC method. It has been known for some time that the manner in which a cigarette is smoked influences the amount of blood nicotine [62]. Although the smoke that leaves the cigarette may be known by machine-based methods, how the smoker inhales it is up to each individual. This includes many complex interwoven factors such as puff volume and frequency, and inhalation depth and duration, as well as physiological parameters. Yet, means for the different product groups studied demonstrate that lower FTC yield cigarettes result in less nicotine uptake per 24 h period, and also per cigarette smoked, than higher FTC yield cigarettes. This result is in contrast to that found by Benowitz and Jacob in a study of 22 smokers using blood nicotine as a determinant of nicotine uptake [53]. They reported no significant correlation with FTC yields and nicotine uptake on a daily or per cigarette basis. One explanation for this disparity could lie in the use of smokers not in their normal environment and unable to perform true ad libitum smoking. Another difference in these studies is the relative ranges of FTC smoker yields studied. Their range of smokers varied approximately 2-fold (0.87 to 1.80 mg/cigarette FTC) while our study covered a 10-fold range (0.13 to 1.30 mg/cigarette FTC). Even if the 1MG smokers were not included, our data would still show a positive increase in Figure 2 with plots of individual smokers having significant slopes ($P<0.05$). A third reason for this disparity in nicotine uptake may lie in the different approaches used to quantify nicotine uptake and only direct comparison on the same subjects would address that issue.

On the other hand, our results are similar to those of Rosa et al. [63] who studied steady-state cotinine levels in 125 smokers. That study examined smokers of cigarettes with

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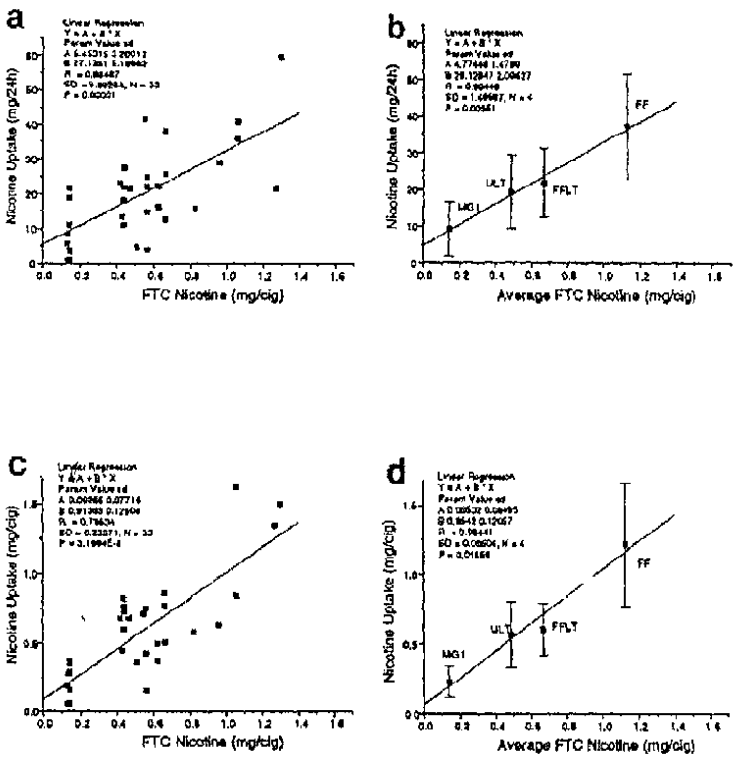

Figure 2. Plots of nicotine uptake versus FTC yield: a) mg/24 h for individual smokers, b) mg/24 h for group averages, c) mg/cigarette for individual smokers, and d) mg/cigarette for group averages. The error bars in b) and d) represent one standard deviation unit on either side of the mean.

machine yields of 0.38-1.38 mg nicotine per cigarette and found a linear correlation between predicted nicotine uptake and serum cotinine which is based on the established linear relationship between nicotine infusion and steady-state plasma cotinine [57].

While differences in FTC yields and measured nicotine uptake are not significant, the ratios of the two in Table II do indicate that the FTC method is not as accurate for predicting nicotine uptake from the lowest yield cigarettes. The FTC

method for determining cigarette "tar" and nicotine yields was intended to compare products and not people. Recent notoriety of this issue has led to speculations that the FTC method is misleading [64, 65]. Our data show the utility of the FTC method as a means of standardizing product yields for comparison. We conclude from our data that, while FTC yield cannot precisely predict nicotine uptake for an individual smoker, it is useful in predicting and comparing actual nicotine uptake by smokers who select cigarettes with a particular FTC yield. The positive slopes in Figure 2 illustrate this point.

Our data for 1MG smokers are similar to those reported by Benowitz et al. [66] for ultra-low yield cigarette smokers (which correspond to the 1MG smokers in our study). There is a considerable decrease in nicotine uptake, especially on a per cigarette basis, for these smokers when compared to smokers of higher yield cigarettes. Höfer et al. [67] also noted this same trend with ultra-low yield smokers, reaching the conclusion that lower yield cigarettes are associated with reduced smoke absorption. The lowest yield cigarettes in particular are apparently very limited in their smoke yield and only by smoking more cigarettes do these smokers obtain nicotine uptake comparable to the other smokers. In our 1MG group, only 2 of 9 got nicotine uptake similar to the ULT and FFLT averages for daily nicotine uptake and both smoked a number of cigarettes far above the average in this study.

Smokers seek a standard for comparison of cigarettes to make informed choices. The FTC method, while not necessarily predictive of nicotine uptake for an individual smoker, is predictive of average nicotine uptake across "tar" categories. Consequently, it is a useful standard for comparison of cigarettes by smokers.

ACKNOWLEDGEMENT

We would like to thank Walter T. Morgan for his assistance with the statistics.

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